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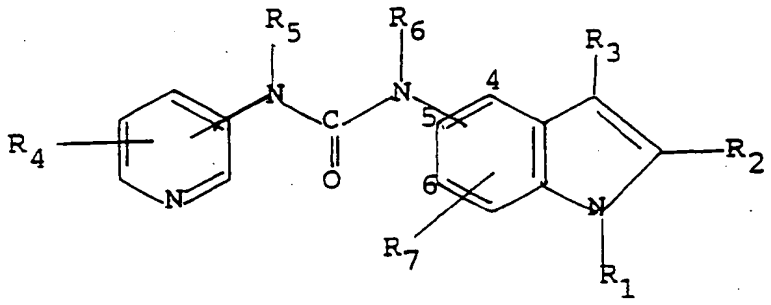
(54) Title: INDOLE UREAS AS 5-HT_{1C} RECEPTOR ANTOGONISTS



(I)

(57) Abstract

Indole ureas of formula (I) or a pharmaceutically acceptable salt thereof wherein: R_1, R_2 and R_3 are independently hydrogen or C_{1-6}alkyl; R_4 is hydrogen, C_{1-6}alkyl, halogen, hydroxy or NR_8R_9 where R_8 and R_9 are independently hydrogen or C_{1-6}alkyl; R_5 and R_6 are independently hydrogen or C_{1-6}alkyl; and R_7 is hydrogen, C_{1-6}alkyl or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6- position of the indole ring. The compounds have $5HT_{1C}$ receptor antagonist activity.

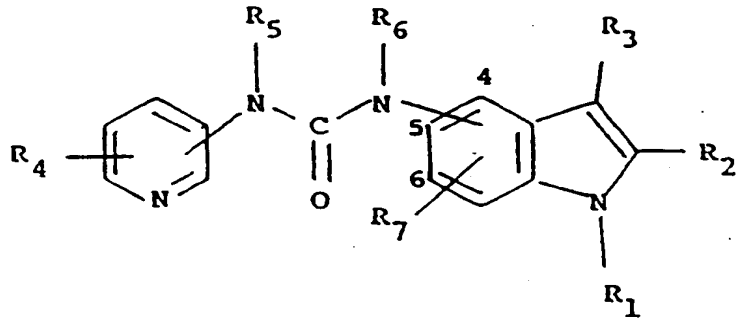
INDOLE UREAS AS 5-HT_{1C} RECEPTOR ANTAGONISTS

This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

P. Fludzinski et. al., J. Med. Chem. 1986 29 2415-2418 describes N-(1,2-dimethyl-3-ethyl-1H-indol-5-yl)-N'-(3-trifluoromethylphenyl)urea which shows selectivity for the rat stomach fundus serotonin receptor.

A class of compounds has now been discovered, which compounds have been found to have $5HT_{1C}$ receptor antagonist activity. $5HT_{1C}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia.

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

lactic, mandelic, tartaric and methanesulphonic.

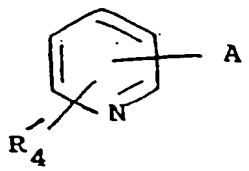
Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes solvates thereof.

When R_5 and/or R_6 are hydrogen or when R_4 is 2- or 4-hydroxy or NR_8R_9 and at least one of R_8 and R_9 are hydrogen the compounds of formula (I) may exist tautomerically in more than one form. The invention extends to each of these forms and mixtures thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

(a) the coupling of a compound of formula (II);



(II)

substituted by R_1', R_2' and R_3' as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5', R_6' and R_7' when other than R_1, R_2, R_3, R_4, R_5, R_6 and R_7, to R_1, R_2, R_3, R_4, R_5, R_6 and R_7, interconverting R_1, R_2, R_3, R_4, R_5, R_6 and R_7 and forming a pharmaceutically acceptable salt.

Suitable examples of groups A and B are

(i) A is -N=C=O and B is $-NHR_6'$,
(ii) A is $-NHR_5'$ and B is -N=C=O,
(iii) A is $-NR_5'COL$ and B is $-NHR_6'$,
(iv) A is $-NHR_5'$ and B is $-NR_6'COL$, or
(v) A is halogen and B is $-NR_6'CONHR_5'$,

wherein R_5' and R_6' are as defined above and L is a leaving group. Examples of suitable leaving groups L include halogen such as chloro or bromo, imidazole, or phenoxy or phenylthio optionally substituted for example with halogen.

When A is -N=C=O and B is NHR_6' or when A is NHR_5' and B is -N=C=O the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

When A is $-NR_5'COL$ and B is $-NHR_6'$ or when A is $-NHR_5'$ and B is $-NR_6'COL$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and B is $-NR_6'CONHR_5'$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

In reaction variant (viii) (Japp-Klingemann synthesis) the compound of formula (IV) is prepared from the aminophenyl urea by diazotisation followed by treatment for example with $CH_3COCH(CO_2X)-CH_2R_3'$ where X is C_{1-6} alkyl under basic conditions in aqueous alcohol as solvent.

The product of formula (IV) may then be cyclised as in the Fischer synthesis above.

In reaction variant (ix) (Madelung synthesis) the compound of formula (IV) is cyclised with base in an inert solvent optionally with heating.

Suitable examples of groups R_2', R_3', R_4', and R_7' which are convertible to R_2, R_3, R_4, and R_7 respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent and alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When R_4 is hydroxy it is preferably protected in the compound of formula (II) as, for example, an aryloxy group such as benzyloxy which is removed by hydrogenation.

Suitable examples of a group R_1' which is convertible to R_1, include typical N-protecting groups such as alkoxycarbonyl, in particular t-butyloxycarbonyl, acetyl, trifluoroacetyl, benzyl and para-methoxybenzyl which are converted to R_1 hydrogen using conventional conditions.

Suitable examples of groups R_5' and R_6' which are convertible to R_5 and R_6 respectively include alkoxycarbonyl and benzyl or para-methoxybenzyl which are converted to R_5 and/or R_6 hydrogen using conventional conditions.

2-amino and R_4' is 3-benzyloxy are commercially available from the Aldrich Chemical Company in the UK. R_5' C_{1-6} alkyl groups may be introduced conventionally, for example by reductive alkylation or acylation and reduction.

Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov et al, Helv. Chim. Acta 1987 70 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) in which A is $-NR_5'COL$ may be prepared by reacting a compound of formula (II) in which A is $-NHR_5'$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

Compounds of formula (II) in which A is halogen and R_4' is hydrogen are commercially available.

Compounds of formula (III) in which B is NHR_6' are known compounds or can be prepared analogously to known compounds, for example by reduction of the corresponding nitroindole by catalytic hydrogenation over Pd/C by the method of P. Fludzinski et al J. Med. Chem., 1986, 29 2415.
Specifically, the compound of formula (III) in which R_1' and R_2' are methyl, R_3' is ethyl, R_6' and R_7' are hydrogen and B

presence of one equivalent of a base such as triethylamine.

Compounds of formula (III) in which B is $-NR_6'CONHR_5'$ can be prepared from the corresponding precursor where B is NHR_6' by reaction with an R_5' isocyanate under conventional conditions.

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

Novel intermediates of formula (III) also form part of the invention.

Compounds of formula (IV) may be prepared from the appropriate aminophenyl derivative analogously to compounds of formula (I). Intermediates of formula (IV) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{1C}$ receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia. Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia,

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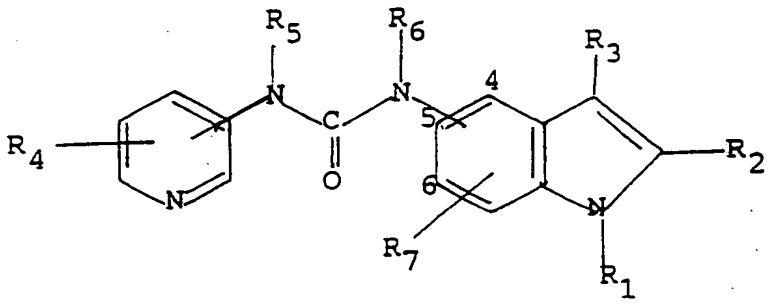

(I)

(57) Abstract

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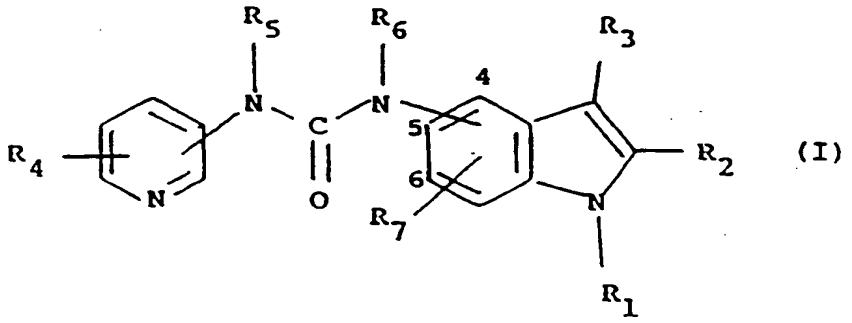


(I)

wherein:

R_1, R_2 and R_3 are independently hydrogen or C_{1-6} alkyl;
R_4 is hydrogen, C_{1-6} alkyl, halogen, hydroxy or NR_8R_9 where R_8 and R_9 are independently hydrogen or C_{1-6} alkyl;
R_5 and R_6 are independently hydrogen or C_{1-6} alkyl; and
R_7 is hydrogen, C_{1-6} alkyl or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole ring.

Alkyl moieties within the variables R_1 to R_9 are preferably C_{1-3} alkyl, such as methyl, ethyl, n- and iso- propyl, most preferably methyl, ethyl and n-propyl.

Suitable R_4 and R_7 halogens include chloro and bromo.

Examples of R_1 include hydrogen, methyl, ethyl and n-propyl, preferably methyl. R_2 is preferably methyl or hydrogen and R_3 is hydrogen, methyl, ethyl, n-propyl, iso-propyl or n-hexyl.

Preferably R_4 is hydrogen, chloro, hydroxy or dimethylamino, most preferably hydrogen.

Preferably R_5, R_6 and R_7 are independently hydrogen or methyl.

The urea moiety may be attached at the 2-, 3-, 4-, 5- or 6-position of the pyridine ring, preferably the 3-, 4- or 5-position.

The urea moiety is preferably attached at the 4- or 5-position of the indole ring.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric,

lactic, mandelic, tartaric and methanesulphonic.

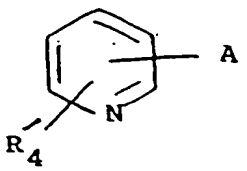
Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes solvates thereof.

When R_5 and/or R_6 are hydrogen or when R_4 is 2- or 4-hydroxy or NR_8R_9 and at least one of R_8 and R_9 are hydrogen the compounds of formula (I) may exist tautomerically in more than one form. The invention extends to each of these forms and mixtures thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

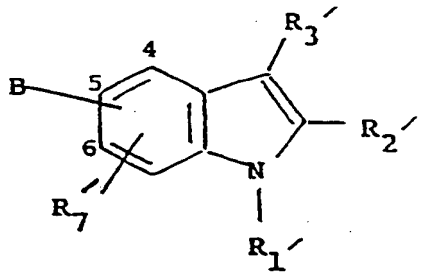
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

(a) the coupling of a compound of formula (II);



(II)

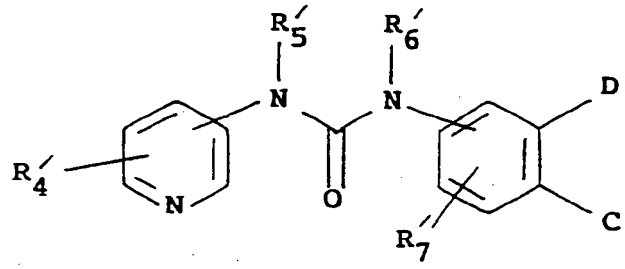
with a compound of formula (III);



(III)

wherein B is attached at the 4-, 5- or 6-position of the indole ring and A and B contain the appropriate functional group(s) necessary to form the moiety $-NR_5'CONR_6'-$ when coupled, wherein R_5' and R_6' are R_5 and R_6 as defined in formula (I) or groups convertible thereto, and the variables R_1', R_2', R_3', R_4' and R_7' are R_1, R_2, R_3, R_4 and R_7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5', R_6' and R_7' when other than R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively to R_1, R_2, R_3, R_4, R_5, R_6 and R_7, interconverting R_1, R_2, R_3, R_4, R_5, R_6 and R_7, and forming a pharmaceutically acceptable salt thereof, or

(b) cyclising a compound of formula (IV):



(IV)

wherein R_4', R_5', R_6' and R_7' are as defined in formulae (II) and (III) and C and D contain the appropriate functional group(s) necessary to form the indole ring

substituted by R_1', R_2' and R_3' as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5', R_6' and R_7' when other than R_1, R_2, R_3, R_4, R_5, R_6 and R_7, to R_1, R_2, R_3, R_4, R_5, R_6 and R_7, interconverting R_1, R_2, R_3, R_4, R_5, R_6 and R_7 and forming a pharmaceutically acceptable salt.

Suitable examples of groups A and B are

(i) A is -N=C=O and B is $-NHR_6'$,
(ii) A is $-NHR_5'$ and B is -N=C=O,
(iii) A is $-NR_5'COL$ and B is $-NHR_6'$,
(iv) A is $-NHR_5'$ and B is $-NR_6'COL$, or
(v) A is halogen and B is $-NR_6'CONHR_5'$,

wherein R_5' and R_6' are as defined above and L is a leaving group. Examples of suitable leaving groups L include halogen such as chloro or bromo, imidazole, or phenoxy or phenylthio optionally substituted for example with halogen.

When A is -N=C=O and B is NHR_6' or when A is NHR_5' and B is -N=C=O the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

When A is $-NR_5'COL$ and B is $-NHR_6'$ or when A is $-NHR_5'$ and B is $-NR_6'COL$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and B is $-NR_6'CONHR_5'$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

The cyclisation of the compound of formula (IV) may be effected using standard methodology such as described in Comprehensive Heterocyclic Chemistry 1984 4, 313 et. seq. or J. Het. Chem. 1988 25 p.1 et seq.

Examples of the more important routes include the Leimgruber synthesis, the Fischer synthesis and the Japp-Klingemann variation and the Madelung synthesis.

Examples of the groups C and D thus include

(vi) C = NO_2 and D = $CH=CH-NZ_2$ where each Z is independently C_{1-6} alkyl or together represent C_{2-7} alkylene;

(vii) C = $NR_1'-N=C(R_2')-CH_2R_3'$ and D = H;

(viii) C = $NH-N=C(CO_2X)-CH_2R_3'$ and D = H where X is C_{1-6} alkyl; and

(ix) C = $NR_1'COR_2'$ and D = CH_2R_3'.

In reaction variant (vi) (Leimgruber synthesis) the compound of formula (IV) is prepared from the 2-methylnitrophenyl urea by treatment with a dialkylacetal of the dialkylformamide $OHCNZ_2$ with heating and the product of formula (IV) cyclised by hydrogenation over a suitable catalyst such as palladium and charcoal optionally under pressure to yield the compound of formula (I) where $R_1=R_2=R_3=H$.

In reaction variant (vii) (Fischer synthesis) the compound of formula (IV) is prepared from the hydrazinophenyl urea by dehydration, preferably by heating, with the appropriate ketone $R_2'COCH_2R_3'$ and the product of formula (IV) cyclised by heating with an acid catalyst such as hydrochloric or sulphuric acid.

In reaction variant (viii) (Japp-Klingemann synthesis) the compound of formula (IV) is prepared from the aminophenyl urea by diazotisation followed by treatment for example with $CH_3COCH(CO_2X)-CH_2R_3'$ where X is C_{1-6} alkyl under basic conditions in aqueous alcohol as solvent.

The product of formula (IV) may then be cyclised as in the Fischer synthesis above.

In reaction variant (ix) (Madelung synthesis) the compound of formula (IV) is cyclised with base in an inert solvent optionally with heating.

Suitable examples of groups R_2', R_3', R_4', and R_7' which are convertible to R_2, R_3, R_4, and R_7 respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent and alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When R_4 is hydroxy it is preferably protected in the compound of formula (II) as, for example, an aryloxy group such as benzyloxy which is removed by hydrogenation.

Suitable examples of a group R_1' which is convertible to R_1, include typical N-protecting groups such as alkoxycarbonyl, in particular t-butyloxycarbonyl, acetyl, trifluoroacetyl, benzyl and para-methoxybenzyl which are converted to R_1 hydrogen using conventional conditions.

Suitable examples of groups R_5' and R_6' which are convertible to R_5 and R_6 respectively include alkoxycarbonyl and benzyl or para-methoxybenzyl which are converted to R_5 and/or R_6 hydrogen using conventional conditions.

Interconversions of R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are carried out by conventional procedures. For example, in the case wherein R_1, R_2 and R_3 are C_{1-6} alkyl and R_5 and R_6 are hydrogen it is possible to introduce a C_{1-6} alkyl group at both the R_5 and R_6 positions by conventional alkylation using 2 molar equivalents of a C_{1-6} alkyl halide and 2 molar equivalents of a suitable base in an inert solvent. Monoalkylation can be achieved using 1 molar equivalent of a C_{1-6} alkyl halide and base using conventional conditions. R_1 C_{1-6} alkyl groups may also be introduced by conventional alkylation, for example using a C_{1-6} alkyl halide and base such as sodium hydride.

R_4 halo and R_7 halo may be introduced by selective halogenation of the pyridine ring or indole ring respectively using conventional conditions.

It should be appreciated that it may be necessary to protect any R_1 to R_7 hydrogen variables which are not required to be interconverted.

Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

It is preferable, however, to introduce and interconvert the groups R_1 to R_7 before coupling compounds of formulae (II) and (III) together, or cyclising the compound of formula (IV).

Compounds of formula (II) in which A is NHR_5' are known compounds or can be prepared analogously to known compounds. For example, the compounds of formula (II) in which A is 3-amino and R_4' is hydrogen, 2-chloro or 6-chloro, and A is

2-amino and R_4' is 3-benzyloxy are commercially available from the Aldrich Chemical Company in the UK. R_5' C_{1-6} alkyl groups may be introduced conventionally, for example by reductive alkylation or acylation and reduction.

Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov et al, Helv. Chim. Acta 1987 70 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) in which A is $-NR_5'COL$ may be prepared by reacting a compound of formula (II) in which A is $-NHR_5'$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

Compounds of formula (II) in which A is halogen and R_4' is hydrogen are commercially available.

Compounds of formula (III) in which B is NHR_6' are known compounds or can be prepared analogously to known compounds, for example by reduction of the corresponding nitroindole by catalytic hydrogenation over Pd/C by the method of P. Fludzinski et al J. Med. Chem., 1986, 29 2415. Specifically, the compound of formula (III) in which R_1' and R_2' are methyl, R_3' is ethyl, R_6' and R_7' are hydrogen and B

is NH_2 is prepared using a procedure similar to that described by Fludzinski.

The nitroindoles are commercially available, for example 5-nitroindole, or may be prepared conventionally (Comprehensive Heterocyclic Chemistry Vol. 4 p. 313 et. seq. (Pergamon Press 1984) and J. Het. Chem. 1988 25 p.1 et. seq.)

An R_2' alkoxycarbonyl group may be eliminated to give R_2' hydrogen, generally under the conditions effecting formation of the nitroindole or as a subsequent step in the process.

R_6' alkyl groups may be introduced conventionally, for example by reductive alkylation or acylation and reduction. R_7' C_{1-6} alkyl groups may be introduced ortho to a nitro substituent by alkylation using a procedure similar to that described in G. Bartoli et. al., J. Org. Chem. 1986 51 3694 and Tetrahedron 1987 43 4221.

Compounds of formula (III) in which B is -N=C=O may be prepared by treating a compound of formula (III) in which :

i) B is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) B is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions.

iii) B is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (III) in which B is $-NR_6'COL$ may be prepared by reacting a compound of formula (III) in which B is $-NHR_6'$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the

presence of one equivalent of a base such as triethylamine.

Compounds of formula (III) in which B is $-NR_6'CONHR_5'$ can be prepared from the corresponding precursor where B is NHR_6' by reaction with an R_5' isocyanate under conventional conditions.

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

Novel intermediates of formula (III) also form part of the invention.

Compounds of formula (IV) may be prepared from the appropriate aminophenyl derivative analogously to compounds of formula (I). Intermediates of formula (IV) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{1C}$ receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia. Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia,

panic attacks, withdrawal from drug abuse and/or schizophrenia.

The invention further provides a method of treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as

binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The following Descriptions illustrate the preparation of intermediates to compounds of the present invention.

Description 1

5-Amino-1,2-dimethyl-3-ethyl-1H-indole (D1)

The title compound was prepared using a procedure similar to that described by P. Fludzinski et al in J. Med. Chem., 1986, 29,2415.

Description 2

1-Methyl-5-nitro-1H-indole (D2)

To a stirred suspension of sodium hydride (5.0g; 167 mM) in dimethylformamide (200 ml) at 0°C under nitrogen was added 5-nitroindole (25g; 154 mM) in dimethylformamide. After stirring for 0.5h, iodomethane (10.5ml; 168mM) in dimethylformamide (50 ml) was added, and stirring was continued for 2h. The reaction mixture was then quenched with water, and poured onto excess water with stirring. Filtration afforded the title compound (27.4g; 94%).

NMR ($CDCl_3$) δ:

3.88 (3H, s), 6.68 (1H, d, J=3) 7.21 (1H, d, J=3) 7.34 (1H, d, J=8) 8.13 (1H, dd, J=8, 2) 8.59 (1H, d, J=2).

Description 3

5-Amino-1-methyl-1H-indole (D3)

A mixture of the nitroindole (D2) (5g; 28.4 mM) and 5% palladium on charcoal in ethanol (300 ml) was hydrogenated at 60 p.s.i. (4.14×10^5Pa) at room temperature for 3h. Removal of the catalyst by filtration followed by

evaporation of the solvent gave the title compound (3.39g; 95%).

NMR ($CDCl_3$) δ:

3.20 (2H, broad s), 3.70 (3H, s), 6.28 (1H, d, J=3) 6.68 (1H, dd, J=8, 2), 6.92 (1H, d, J=2), 6.96 (1H, d, J=3), 7.12 (1H, d, J=8)

Description 4

3-Pyridyl isocyanate (D4)

The title compound was prepared from 3-pyridinecarbonyl azide in toluene using a procedure similar to that described by L.S. Trifonov et al in Helv. Chim. Acta, 1987, 70, 262.

Description 5

5-Nitro-1,2,3-trimethyl-1H-indole (D5)

The title compound was prepared in 99% yield from 2,3-dimethyl-5-nitroindole using a procedure similar to that in Description 2.

NMR ($CDCl_3$) δ:

2.28 (3H, s), 2.38 (3H, s), 3.71 (3H, s), 7.22 (1H, d, J=8), 8.06 (1H, dd, J=8, 2), 8.46 (1H, d, J=2).

Description 6

5-Amino-1,2,3-trimethyl-1H-indole (D6)

The title compound was prepared in 91% yield from the nitroindole (D5) using a procedure similar to that in Description 3.

NMR ($CDCl_3$) δ:

2.18 (3H, s), 2.29 (3H, s), 3.00 (2H broad s), 3.57 (3H, s), 6.60 (1H, dd, J=8, 2) 6.80 (1H, d, J=2), 7.03 (1H, d, J=8).

Description 7

5-Nitro-1-propyl-1H-indole (D7)

The title compound was prepared in 96% yield from 5-nitroindole and propyl iodide using a procedure similar to that in Description 2.

NMR ($CDCl_3$) δ:

0.96 (3H, t, J=7), 1.90 (2H, h, J=7), 4.13 (2H, t, J=7), 6.68 (1H, d, J=3), 7.26 (1H, d, J=3), 7.37 (1H, d, J=8), 8.10 (1H, dd, J=8, 2), 8.59 (1H, d, J=2).

Description 8

5-Amino-1-propyl-1H-indole (D8)

The title compound was prepared in 100% yield from the nitroindole (D7) using a procedure similar to that in Description 3.

NMR ($CDCl_3$) δ:

0.91 (3H, t, J=7, 1.83 (2H, h, J=7), 3.38 (2H, broad s), 4.02 (2H, t, J=7), 6.29 (1H, d, J=3), 6.68 (1H, dd, J=8, 2), 6.93 (1H, d, J=2), 7.01 (1H, d, J=3), 7.14 (1H, d, J=8).

Description 9

1-Methyl-4-nitro-1H-indole (D9)

To a stirred suspension of sodium hydride (0.14g; 3.41 mM) in dimethylformamide (10 ml) at 0°C under nitrogen was added 4-nitroindole (0.5g; 3.1 mM) in dimethylformamide. After stirring for 0.5h, iodomethane (0.21 ml; 3.41 mM) in dimethylformamide (1 ml) was added, and stirring was continued for 1h. The reaction mixture was then quenched with water, and poured onto excess water with stirring. Filtration afforded the title compound (0.5g; 92%).

NMR ($CDCl_3$ δ:

3.89 (3H, s), 7.30 (3H, m), 7.66 (1H, d, J=8), 8.15 (1H, d, J=8).

Description 10

4-Amino-1-methyl-1H-indole (D10)

A mixture of the nitroindole (D9) (0.5g; 2.8 mM) and 5% palladium on charcoal in ethanol (75 ml) was hydrogenated at 60 p.s.i. (4.14×10^5 Pa) at room temperature for 2h. Removal of the catalyst by filtration followed by evaporation of the solvent gave the title compound (0.44g; 97%).

NMR ($CDCl_3$) δ:

3.76 (3H, s), 6.42 (1H, d, J=2), 6.45 (1H, d, J=8), 6.81 (1H, d, J=8), 6.96 (1H, d, J=2), 7.05 (1H, t, J=8).

Description 11

1-Methyl-6-nitro-1H-indole (D11)

To a solution of sodium hydride (0.27g; 6.8mM) in dimethylformamide (4 ml) at 0°C under nitrogen, was added 6-nitroindole (1g; 6.2mM) in dimethylformamide (12 ml). After stirring at room temperature for 0.5h, iodomethane (0.42 ml; 6.8 mM) in dimethylformamide (1 ml) was added and stirring continued for 1h. The reaction mixture was then quenched with water, and poured onto excess water with stirring. Filtration afforded the title compound (1.03g; 94%).

NMR ($CDCl_3$) δ:

3.60 (3H, s), 6.60 (1H, d, J=4), 7.35 (1H, d, J=4), 7.55 (1H, d, J=10), 8.10 (1H, dd, J=10, 2), 8.34 (1H, d, J=2)

Description 12

6-Amino-1-methyl-1H-indole (D12)

A mixture of the nitroindole (D11) (0.8g; 4.55 mM) and 5% palladium on charcoal in ethanol (150 ml) was hydrogenated at 60 p.s.i. (4.14×10^5 Pa) at room temperature for 2h. Removal of the catalyst by filtration followed by evaporation of the solvent gave the crude product.

Chromatography on silica using dichloromethane as eluant afforded the title compound (0.3g; 45%).

NMR ($CDCl_3$) δ:

3.68 (3H, s), 6.38 (1H, d, J=3), 6.55-6.65 (2H, m), 6.88 (1H, d, J=3), 7.40 (1H, s, J=10).

Description D13

3-Methylaminopyridine (D13)

A mixture of 3-aminopyridine (5.76g; 60 mM) in triethylorthoformate (49 ml) was refluxed with stirring for 5h. The excess solvent was removed in vacuo to give an oil (8.53g, 93%). The oil was dissolved in ethanol (30 ml) and cooled in ice. To this solution was added sodium borohydride (2.58g, 68.3 mM) portionwise and left to stir at room temperature for 17h. The solution was cooled in an ice bath, and water added slowly (3 ml), followed by 5N HCl until no further evolution of gas was observed. The pH was adjusted to 7, then extracted using ethyl acetate, washed with water, dried and evaporated to give an oil (5.10g; 83%). Chromatography on silica using dichloromethane as eluant afforded the title compound (1.43g; 22%).

NMR ($CDCl_3$) δ: 2.82 (3H, s), 4.12 (1H, s), 6.87 (1H, dd, J=8,3), 7.09 (1H, m), 7.95 (1H, dd, J=3,1), 8.02 (1H, d, J=3).

Description 14

N-(1-Methyl-1H-indol-5-yl)formamide (D14)

To acetic anhydride (1.68 ml; 15 mM) at 0°C was added 98% formic acid (0.8 ml; 21 mM) dropwise under a nitrogen atmosphere, to generate acetic formic anhydride. The solution was heated at 50-60°C for 2h then cooled to room temperature. Dichloromethane (2 ml) was added and the solution was cooled to -20°C before adding a solution of aminoindole (D3) (1g, 6.88 mM) in dichloromethane (4 ml). The mixture was stirred at room temperature for 17h then evaporated to dryness to give a brown oil (1.34g) Chromatography on silica using ethyl acetate as eluant afforded the title compound (1.05g; 88%).

NMR ($CDCl_3$) δ: Complex spectrum due to amide isomers

Found: M^+ 174

$C_{10}H_{10}N_2O$ requires 174

Description 15

1-Methyl-5-methylamino-1H-indole (D15)

To a suspension of lithium aluminium hydride (0.33g; 8.7 mM) in dry tetrahydrofuran (15 ml) at 0°C under a nitrogen atmosphere was added the amide (D14) (1.0g; 5.74 mM). The solution was left to stir at room temperature for 17h, cooled to 0°C and then water (3.5 ml), 5N sodium hydroxide solution (3.5 ml) and then water (5 ml) added in that order. The solution was left to stir for 10 min, then filtered and evaporated to give a brown oil (0.89g). Chromatography on silica using dichloromethane as eluant gave the title compound (0.57g; 62%).

NMR ($CDCl_3$) δ: 2.9 (3H, s), 3.52 (1H, s), 3.73 (3H, s), 6.33 (1H, d, J=3), 6.69 (1H, dd, J=8,1), 6.87 (1H, d, J=1), 6.97 (1H, d, J=3), 7.16 (1H, d, J=8).

Description 16

1,4-Dimethyl-5-nitroindole (D16)

The title compound was prepared from 1-methyl-5-nitroindole (D2) using a procedure similar to that described by G.Bartoli et al in J.Org.Chem. 1986, 51, 3694 and Tetrahedron 1987, 43, 4221. This gave a yellow solid, m.p. 120-3°C, in 64% yield.

NMR ($CDCl_3$) δ: 2.84 (3H, s), 3.83 (3H, s), 6.71 (1H, d, J=3), 7.18 (1H, d, J=3), 7.20 (1H, d, J=8), 7.99 (1H, d, J=8).

Found: M^+ 190

$C_{10}H_{10}N_2O_2$ requires 190

Found: C, 63.0; H, 5.3; N, 14.6%. $C_{10}H_{10}N_2O_2$ requires C, 63.1; H, 5.3; N, 14.7%

Description 17

5-Amino-1,4-dimethylindole (D17)

The title compound was prepared from 1,4-dimethyl-5-nitroindole (D16) by catalytic hydrogenation as described in Description 3. This gave a dark purple oil in 92% yield.

NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.1 (2H, bs), 3.72 (3H, s), 6.37 (1H, d, J=3), 6.71 (1H, d, J=8), 6.98 (1H, d, J=3), 7.02 (1H, d, J=8).

Description 18

N-(1-Methyl-1H-indol-5-yl)-N'-(3-benzyloxypyrid-2-yl)urea (D18)

The title compound was prepared from 5-amino-1-methyl-1H-indole (D3), carbonyl diimidazole and 2-amino-3-benzyloxypyridine using a procedure similar to that described in Example 1.

NMR (D_6-DMSO) δ: 3.80 (3H, s), 5.44 (2H, s), 6.40 (1H, d, J=6), 7.35 (7H, m), 7.61 (2H, dd, J=13,3), 7.80 (2H, d, J=3), 7.94 (2H, d, J=6).

Description 19

3-Ethyl-2-methyl-5-nitro-1H-indole (D19)

The title compound was prepared using a procedure identical to that described by P. Fludzinski et al in J.Med.Chem., 1986, 29, 2415.

Description 20

1,3-Diethyl-2-methyl-5-nitro-1H-indole (D20)

The title compound was prepared in 92% yield from the nitroindole (D19), sodium hydride, and iodoethane using a procedure similar to that described in Description 2.

NMR ($CDCl_3$) δ: 1.23 (3H, t, J=8), 1.36 (3H, t, J=8), 2.40 (3H, s), 2.73 (2H, q, J=8), 4.12 (2H, q, J=8), 7.21 (1H, d, J=9), 8.02 (1H, dd, J=9, 2), 8.49 (1H, d, J=2).

Description 21

5-Amino-1,3-diethyl-2-methyl-1H-indole (D21)

The title compound was prepared in 86% yield from the nitroindole (D20) using a procedure similar to that in Description 3.

NMR ($CDCl_3$) δ: 1.22 (3H, t, J=8), 1.37 (3H, t, J=8), 2.39 (3H, s), 2.75 (2H, q, J=8), 4.14 (2H, q, J=8), 7.26 (1H, d, J=8), 8.04 (1H, dd, J=8, 1), 8.50 (1H, d, J=1).

Description 22

2-Methyl-5-nitro-3-propyl-1H-indole (D22)

The title compound was prepared in 94% yield from the 4-nitrophenylhydrazone of 2-hexanone using the method of Fludzinski et al described in J.Med. Chem., 1986, 29, 2415.

NMR ($CDCl_3$) δ: 0.94 (3H, t, J=8), 1.65 (2H, m, J=8), 2.38 (3H, s), 2.65 (2H, t, J=8), 7.22 (1H, d, J=9), 7.98 (1H, dd, J=9, 2), 8.15 (1H, s), 8.45 (1H, d, J=2).

Description 23

1,2-Dimethyl-5-nitro-3-propyl-1H-indole (D23)

The title compound was prepared in 89% yield from the nitroindole (D22) using a procedure similar to that in Description 2.

NMR ($CDCl_3$) δ: 0.90 (3H, t, J=8), 1.55 (2H, m, J=8), 2.34 (3H, s), 2.70 (2H, t, J=8), 3.72 (3H, s), 7.55 (1H, d, J=9), 7.92 (1H, dd, J=9, 2), 8.35 (1H, d, J=2).

Description 24

5-Amino-1,2-dimethyl-3-propyl-1H-indole (D24)

The title compound was prepared in 92% yield from the nitroindole (D23) using a procedure similar to that in Description 3.

NMR ($CDCl_3$) δ: 1.10 (3H, t, J=8), 1.75 (2H, m, J=8), 2.42 (3H, s), 2.75 (2H, t, J=8), 3.65 (3H, s), 3.95 (2H, s), 6.65 (1H, d, J=9), 6.92 (1H, s), 7.14 (1H, d, J=9).

Description 25

3-n-Hexyl-2-methyl-5-nitro-1H-indole (D25)

The title compound was prepared in 72% yield from the 4-nitrophenylhydrazone of 2-nonanone using the method of Fludzinski et al described in J.Med.Chem., 1986, 29, 2415.

NMR ($CDCl_3$) δ: 0.90 (3H, m), 1.30 (6H, m), 1.60 (2H, m), 2.42 (3H, s), 2.68 (2H, t, J=7), 7.22 (1H, m), 8.04 (1H, m), 8.20 (1H, s), 8.45 (1H, d, J=1).

Description 26

1,2-Dimethyl-3-n-hexyl-5-nitro-1H-indole (D26)

The title compound was prepared in 74% yield from the nitroindole (D25) using a procedure similar to that in Description 2.

NMR ($CDCl_3$) δ: 0.88 (3H, m), 1.30 (6H, m), 1 58 (2H, m), 2.35 (3H, s), 2.70 (2H, m), 3.65 (3H, s), 7.15 (1H, d, J=9), 7.94 (1H, m), 8.46 (1H, d, J=1).

Description 27

5-Amino-1,2-dimethyl-3-n-hexyl-1H-indole (D27)

The title compound was prepared in 84% yield from the nitroindole (D26) using a procedure similar to that in Description 3.

NMR ($CDCl_3$) δ: 0.88 (3H, m), 1.30 (6H, m), 1.55 (2H, m), 2.28 (3H, s), 2.62 (2H, t, J=8), 2.98 (2H, s), 3.55 (3H, s), 6.58 (1H, m), 6.80 (1H, d, J=1), 7.0 (1H, d, J=8).

Description 28

Ethyl 2-Oxopentanoate (D28)

The sodium salt of 2-oxopentanoic acid (1.00g, 7.25 mM) was taken up in water and acidified to pH 1. The solution was extracted with ethyl acetate (3 x 100 ml), dried and solvents removed in vacuo. The resulting oil (0.67g) was taken up in ethanol (50 ml) and Amberlyst 15 added (0.67g). The suspension was stirred over 48h, the resin filtered off and solvents removed in vacuo to give the title compound as a slightly coloured oil (0.54g; 64%).

NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7), 1.38 (3H, t, J=7), 1.55 (2H, m), 2.32 (2H, t, J=6), 4.32 (2H, q, J=7).

Description 29

Ethyl 2-oxopentanoate 4-nitrophenylhydrazone (D29)

To a solution of the ester (D28) (0.53g, 3.6 mM) in ethanol (20 ml) was added 4-nitrophenylhydrazine (0.56g, 3.6 mM) and the suspension stirred for 0.5h. Concentrated hydrochloric acid (2 ml) was added to give a brown solution. After stirring for 0.5h the solution was cooled in ice and the precipitated title compound filtered off (0.72g; 69%).

NMR ($CDCl_3$) δ: 1.02 (3H, m), 1.40 (3H, m), 1.62 (2H, m), 2.60 (2H, m), 4.32 (2H, m), 7.28 (2H, m), 8.15 (2H, m), 8.30 (1H, s).

Description 30

3-Ethyl-5-nitro-1H-indole (D30)

The 4-nitrophenylhydrazone of ethyl 2-oxopentanoate (D29) (0.72g, 2.60 mM) was heated to reflux for 16h in concentrated hydrochloric acid. After cooling to room temperature the precipitated solid was filtered off. Chromatography on silica using dichloromethane as eluant gave the title compound as a yellow solid (0.22g; 45%).

NMR ($CDCl_3$) δ: 1.35 (3H, t, J=8), 2.80 (2H, q, J=7), 7.12 (1H, m), 7.40 (1H, d, J=10), 8.12 (1H, dd, J=6, 1), 8.44 (1H, s), 8.60 (1H, m).

Description 31

3-Ethyl-1-methyl-5-nitro-1H-indole (D31)

The title compound was prepared in 95% yield from the corresponding indole (D30) following a procedure similar to that in Description 2.

NMR ($CDCl_3$) δ: 1.3 (3H, t, J=7), 2.0 (2H, q, J=7), 3.82 (3H, s), 6.98 (1H, s), 7.27 (1H, d, J=8), 8.12 (1H, dd, J=7, 1), 8.55 (1H, d, J=1).

Found: M^+ 204

$C_{16}H_{12}N_2O_2$ requires 204.

Description 32

5-Amino-3-ethyl-1-methyl-1H-indole (D32)

The title compound was prepared from the corresponding nitro-indole (D31) in 98% yield following a procedure similar to that in Description 3.

NMR ($CDCl_3$) δ: 1.25 (3H, m), 2.70 (2H, q, J=8), 3.64 (3H, s), 6.62 (1H, m), 6.71 (1H, s), 6.78 (1H, m), 7.06 (1H, m).

Description 33

Phenyl N-(1-Methyl-1H-indol-5-yl)carbamate (D33)

To a solution of phenyl chloroformate (2.21 ml; 17.4 mM) in dry tetrahydrofuran (30 ml), cooled in a carbon tetrachloride / solid carbon dioxide bath, was added 5-amino-1-methylindole (D3) (2.31g; 15.8 mM) followed by triethylamine (2.40 ml; 17.4 mM). The mixture was stirred for 45 min at -20°C (bath temp.), then evaporated and the residue was dissolved in ethyl acetate, washed with brine, dried and evaporated to give the title compound (4.29g; 100%), m.p. 103-107°C (EtOAc/petrol).

NMR ($CDCl_3$) δ: 3.80 (3H, s), 6.45 (1H, d, J=3), 6.93 (1H, broad s), 7.05 (1H, d, J=3), 7.25 (5H, m), 7.40 (2H, dd, J=8, 8), 7.74 (1H, broad s).

Description 34

2-Dimethylamino-5-nitropyridine (D34)

2-Chloro-5-nitropyridine (1.58g, 10 mM) was treated with a 33% w/w solution of dimethylamine in methylated spirit (18 ml, 100 mM). An exothermic reaction ensued, with formation of a yellow solid. After 0.5h the solid was filtered off. The filtrate was evaporated and the residue was combined with the yellow solid, and all material was dissolved in dichloromethane. This solution was washed with water and brine, dried and evaporated, to give the title compound (1.64g; 98%), m.p. 146-149°C.

NMR ($CDCl_3$) δ: 3.25 (6H, s), 6.48 (1H, d, J=10), 8.20 (1H, dd, J=10,3), 9.06 (1H, d, J=3).

Found: M^+ 167

$C_7H_9N_3O_2$ requires 167.

Description 35

5-Amino-2-dimethylaminopyridine (D35)

2-Dimethylamino-5-nitropyridine (D34) (1.64g, 9.8 mM) was stirred with 10% palladium on charcoal (0.16g) in ethanol (200 ml) under 1 atmos. of hydrogen. After 6h the catalyst was filtered off onto Kieselguhr and the filtrate was evaporated. The residue was dissolved in diethyl ether, filtered again, and chromatographed on silica gel (50g) using ether as eluant. The eluted product was purified further by extraction with petrol (bp 60-80°C) to give the title compound as a reddish oil (0.66g; 49%).

NMR ($CDCl_3$) δ: 3.00 (6H, s), 6.47 (1H, d, J=9), 6.99 (1H, dd, J=9,3), 7.78 (1H, d, J=3).

Found: M^+ 137

$C_7H_{11}N_3$ requires 137

Description 36

3-Isopropyl-2-methyl-5-nitro-1H-indole (D36)

The title compound was prepared in 62% yield from the 4-nitrophenyl hydrazone of 4-methyl-2-pentanone using the method of Fludzinski et al described in J. Med. Chem., 1986, 29, 2415.

NMR ($CDCl_3$) δ: 1.42 (6H, d, J=6), 2.42 (3H, s), 3.20 (1H, m), 7.28 (1H, m), 8.03 (1H, dd, J=7,1), 8.12 (1H, s), 8.60 (1H, m).

Description 37

1,2-Dimethyl-3-isopropyl-5-nitro-1H-indole (D37)

The title compound was formed in 85% yield from the nitroindole (D36) following a procedure similar to that in Description 2.

NMR ($CDCl_3$) δ: 1.47 (6H, d, J=7), 2.42 (3H, s), 3.20 (1H, m), 3.68 (3H, s), 7.24 (1H, m), 8.04 (1H, m), 8.62 (1H, m).

Description 38

5-Amino-1,2-dimethyl-3-isopropyl-1H-indole (D38)

The title compound was formed in 57% yield from the nitroindole (D37) following a procedure similar to that in

Description 3.

NMR ($CDCl_3$) δ: 1.35 (6H, d, J=7), 2.30 (3H, s), 3.15 (1H, m), 3.55 (3H, s), 6.60 (1H, m), 7.05 (2H, m).

Example 1

N-(1,2-Dimethyl-3-ethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E1)

To a solution of the aminoindole (D1) (0.71g; 3.78mM) in dichloromethane (13.5ml) at 0°C was added a 12.5% solution of phosgene in toluene (3.28ml; 3.79mM). After stirring for 0.5h, triethylamine (1.15ml) was added and stirring was continued for 0.5h. A solution of 3-aminopyridine (0.34g; 3.6mM) in dichloromethane (10ml) was then added, and stirring continued for 3.5h at room temperature. Several drops of aqueous sodium hydroxide were added to the reaction mixture which was vigorously stirred for 0.5h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulphate and evaporated to dryness. Chromatography on silica using dichloromethane as eluant afforded the title compound (0.2g; 17%) which was converted to the hydrochloride salt using hydrogen chloride in ether/ethanol, m.p. 158-165°C.

NMR (D_6-DMSO) δ:
1.12 (3H, t, J=8), 2.31 (3H, s), 2.63 (2H, q, J=8), 3.61 (3H, s), 7.02 (1H, m), 7.28 (1H, d, J=10), 7.64 (1H, s), 7.89 (1H, m), 8.31 (1H, m), 8.45 (1H, d, J=6), 9.13 (1H, s), 9.22 (1H, s), 10.12 (1H, s).

Found: M^+ 308.1640
$C_{18}H_{20}N_4O$ requires 308.1637

Example 2

N-(1-Methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E2)

Method A

The title compound was prepared from 5-amino-1-methyl-1H-indole(D3), phosgene and 3-aminopyridine using a procedure similar to that described for Example 1, in 27% yield m.p. 175-180°C.

NMR (d_6-DMSO) δ: 3.76 (3H, s), 6.34 (1H, d, J=2), 7.16 (1H, dd, J=8, 2), 7.29 (1H, d, J=2), 7.37 (1H, d, J=8), 7.70 (1H, s), 7.87 (1H, dd, J=8, 8), 8.30 (1H, m), 8.45 (1H, J=8), 9.08 (1H, m), 9.24 (1H, s), 10.03 (1H, s).

Found: M^+ 266.1667

$C_{15}H_{14}N_4O$ requires 266.1667

Method B

A solution of the aminoindole (D3) (1.95g; 13 mM) in dichloromethane (20 ml) was added dropwise to a solution of 3-pyridyl isocyanate (D4) (prepared from 3-pyridinecarbonyl azide (2.14g; 15mM) in toluene) at room temperature. The reaction mixture was stirred for 17h, then cooled, and the precipitate filtered off to give the crude product (3.36g; 95%). This was dissolved in hot ethanol and ethereal hydrogen chloride added to afford the title compound as its hydrochloride salt (3.1g; 80%) identical with the material prepared by method A.

Example 3

N-(1,2,3-Trimethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E3)

The title compound was prepared in 51% yield from 5-amino-1,2,3-trimethyl-1H-indole (D6), phosgene and 3-aminopyridine using a procedure similar to that in Example 1, m.p. 330°C.

NMR (D_6-DMSO) δ:

2.12 (3H, s), 2.30 (3H, s), 3.60 (3H, s), 7.04 (1H, dd, J=9, 2), 7.27 (1H, d, J=9), 7.58 (1H, d, J=2), 7.89 (1H, dd, J=9, 9), 8.32 (1H, m), 8.44 (1H, d, J=6), 9.11 (1H, d, J=2), 9.28 (1H, s), 10.22 (1H, s).

Found: M^+ 294.1485

$C_{17}H_{18}N_4O$ requires: 294.1481

Example 4

N-(1-Propyl-1H-indol-5-yl)-N'-(3-pyridyl)urea oxalate (E4)

The title compound was prepared in 43% yield from 5-amino-1-propyl-1H-indole (D8) and 3-pyridyl isocyanate (D4) using a procedure similar to that in Example 2 (Method B), the product being isolated as the oxalate salt, m.p. 16 -169°C.

NMR (D_6 DMSO) δ:

0.82 (3H, t, J=7), 1.76 (2H, h, J=7), 4.10 (2H, t, J=7),

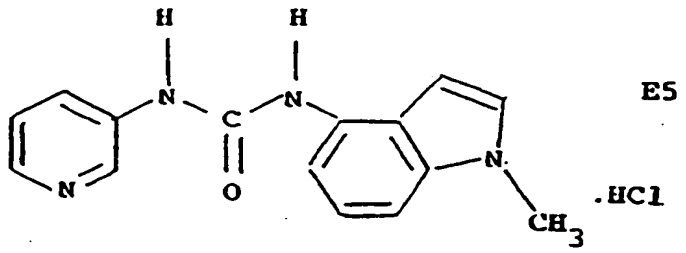
6.37 (1H, d, J=3), 7.13 (1H, d, J=9), 7.34 (1H, d, J=3), 7.40 (1H, d, J=9), 7.44 (1H, m), 7.69 (1H, s), 8.05 (1H, m), 8.24 (1H, d, J=6), 8.67 (1H, s), 8.73 (1H, d, J=2), 8.97 (1H, s).

Found: M^+ 294.1485

$C_{17}H_{18}N_4O$ requires: 294.1481

Example 5

N-(1-Methyl-1H-indol-4-yl)-N'-(3-pyridyl)urea hydrochloride (E5)



E5

A solution of the aminoindole (D10) (0.44g; 3.01 mM) in dichloromethane (10 ml) was added dropwise to a solution of 3-pyridyl isocyanate (D4) (prepared from 3-pyridine carbonyl azide (0.51g; 3.4 mM) in toluene) at room temperature. The reaction mixture was stirred for 17h, then cooled and the precipitate filtered off to give the crude product (1g; 100%). This was dissolved in hot ethanol and ethereal hydrogen chloride added to afford the title compound as its hydrochloride salt (0.74g; 81%), m.p 238°C.

NMR (D_6 DMSO) δ:

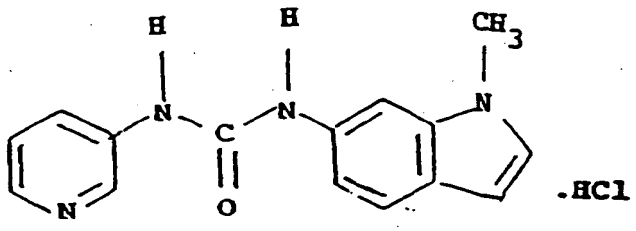
3.79 (3H, s), 6.80 (1H, d, J=3), 7.11 (2H, dd, J=6, 6), 7.30 (1H, d, J=3), 7.70 (1H, dd, J=6, 2), 7.90 (1H, m), 8.33 (1H, d, J=6), 8.49 (1H, d, J=3), 9.13 (1H, d, J=2), 9.40 (1H, s), 10.80 (1H, s).

Found: M^+ 266.1170

$C_{15}H_{14}N_4O$ requires: 266.1167

Example 6

N-(1-Methyl-1H-indol-6-yl)-N'-(3-pyridyl)urea hydrochloride (E6)



.HCl E6

A solution of the aminoindole (D12) (0.3g; 2.05 mM) in dichloromethane (10 ml) was added dropwise to a solution of 3-pyridyl isocyanate (D4) (prepared from 3-pyridinecarbonyl azide (0.28g; 2.26 mM) in toluene) at room temperature. The reaction mixture was stirred for 17h, then cooled, and the precipitate filtered off to give the crude product (0.43g; 79%). This was dissolved in hot ethanol and ethereal hydrogen chloride added to afford the title compound as the hydrochloride salt (0.35g; 56%), m.p. 215°C.

NMR ($CDCl_3$) δ:

3.73 (3H, s), 6.36 (1H, d, J=2), 6.96 (1H, dd, J=11, 2), 7.24 (1H, d, J=2), 7.45 (1H, d, J=11), 7.75 (1H, d, J=3), 7.90 (1H, m), 8.32 (1H, d, J=8), 8.46 (1H, d, J=3), 9.13 (1H, d, J=3), 9.49 (1H, s), 10.25 (1H, s).

Found:	C, 59.24;	H, 4.96;	N, 18.38.
$C_{15}H_{15}N_4OCl$ requires:	C, 59.50;	H, 4.99;	N, 18.51

Example 7

N-(1H-Indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E7)

Method A

A solution of commercially available 5-aminoindole (0.5g; 3.8 mM) in dichloromethane (5 ml) was added dropwise to a solution of 3-pyridyl isocyanate (D4) (prepared from 3-pyridinecarbonyl azide (0.62g; 4.2 mM) in toluene) at room temperature. The reaction mixture was stirred for 2 days, then cooled and the precipitate filtered off, to give the crude product (0.54g; 57%), which was dissolved in ethanol and converted to the hydrochloride salt using hydrogen chloride in ether, m.p. 180-185°C.

NMR (D_6-DMSO) δ:6.38 (1H, s), 7.11 (1H, d, J=8), 7.35 (2H, m), 7.7 (1H, s), 7.92 (1H, m), 8.35 (1H, d, J=8), 8.49 (1H, d, J=3), 9.12 (1H, s), 9.39 (1H, s), 10.41 (1H, s), 11.7 (1H, s).

Found: M^+ 252

$C_{14}H_{12}N_4O$ requires 252

Method B

Compound E7 may also be prepared by reacting 3-methyl-4-nitroaniline with 3-pyridyl isocyanate (D4) by the procedure of Method A. The resulting nitrophenyl urea may be subjected to a Leimgruber synthesis by condensation with dimethylformamide dimethylacetal with heating followed by hydrogenation over palladium and charcoal at high pressure to effect formation of the indole.

Example 8

N-(1-Methyl-1H-indol-5-yl)-N'-methyl-N'-(3-pyridyl)urea (E8)

To a solution of carbonyl diimidazole (1.22g; 7.5 mM) in dichloromethane (10 ml) was added aminoindole (D3) (1.0g; 6.85 mM) in dichloromethane (10 ml). After stirring at room temperature for 15 min, the solution was evaporated to dryness. The residue was taken up in dimethylformamide (10 ml) and to this solution was added 3-methylaminopyridine (D13) (0.74g; 6.2 mM) in dimethylformamide (10 ml). The reaction mixture was heated to 90°C for 1h, then cooled and added dropwise to water (200 ml) with vigorous stirring. After cooling overnight, the precipitate was filtered and dried to give the crude product (1.99g). Chromatography on silica using dichloromethane as eluant afforded the title compound (0.81g; 42%), m.p. 58-60°C.

NMR ($CDCl_3$) δ:3.40 (3H, s), 3.75 (3H, s), 6.18 (1H, d), 6.39 (1H, d, J=3), 7.02 (1H, d, J=3), 7.09 (1H, dd, J=8, 1), 7.21 (1H, d, J=8), 7.42 (1H, m), 7.57 (1H, d, J=1), 7.75 (1H, m), 8.59 (1H, dd, J=3,1), 8.70 (1H, d, J=1).

Found: M^+ 280

$C_{16}H_{16}N_4O$ requires 280

Example 9

N-Methyl-N-(1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E9)

The title compound was prepared from 1-methyl-5-methylamino-1H-indole (D15) and 3-pyridyl isocyanate (D4) using a procedure similar to that described for Example 2 Method B. The crude product was obtained in 45% yield.

Recrystallisation from ethanol afforded the title compound, m.p. 168-170°C.

NMR ($CDCl_3$) δ:3.39 (3H, s), 3.87 (3H, s), 6.35 (1H, s), 6.55 (1H, d, J=3), 7.18 (3H, m), 7.43 (1H, d, J=8), 7.60 (1H, d, J=1), 8.01 (1H, m), 8.2 (2H, m).

Found: C, 68.55; H, 5.79; N, 19.92%
$C_{16}H_{16}N_4O$ requires C, 68.55; H, 5.75; N, 19.99%

Example 10

N-Methyl-N-(1-methyl-1H-indol-5-yl)-N'-methyl-N'-(3-pyridyl)urea (E10)

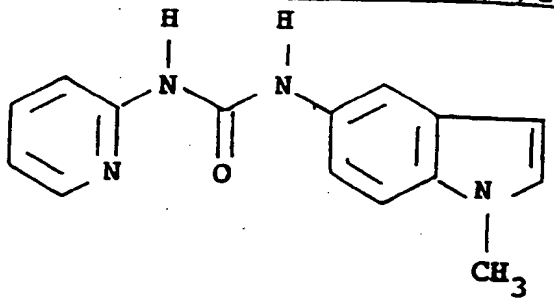
To a suspension of 80% sodium hydride (0.06g; 2 mM) in dimethylformamide (5 ml), was added the monomethyl urea (E9) (0.5g; 1.79 mM). After stirring at room temperature for 0.5h; methyl iodide (0.12 ml; 1.93 mM) was added dropwise. Stirring was continued at room temperature for 1h, then heated at 50°C for 1h. The reaction mixture was cooled in ice, then quenched with water. The mixture was then extracted with dichloromethane, washed with water, dried over sodium sulphate and evaporated to give the crude product (0.59g). Chromatography on silica using dichloromethane as eluant afforded the title compound (0.31g; 60%) which was recrystallised from cyclohexane to give a white solid (160 mg) m.p. 91-92.5°C.

NMR ($CDCl_3$) δ:3.18 (3H, s), 3.25 (3H, s), 3.71 (3H, s), 6.3 (1H, d, J=3), 6.6 (1H, dd, J=8,1), 6.85 (1H, m), 7.01 (4H, m), 8.10 (2H, m).

Found: C, 69.57; H, 6.21; N, 19.04%
$C_{17}H_{18}N_4O$ requires C, 69.37; H, 6.16; N, 19.03%

Example 11

N-(1-Methyl-1H-indol-5-yl)-N'-(2-pyridyl)urea (E11)



E11

The title compound was prepared from 5-amino-1-methylindole (D3) and 2-aminopyridine using a procedure similar to that described for Example 8. The crude product was obtained in 83% yield. Recrystallisation from ethanol afforded the title compound in 70% yield, m.p. 182-185°C.

NMR ($CDCl_3$) δ:3.8 (3H, s), 6.42 (1H, d, J=3), 6.9 (1H, m), 7.05 (1H, d, J=1), 7.2 (1H, d, J=8), 7.25 (1H, d, J=1), 7.32 (1H, dd, J=8, 1), 7.61 (1H, m), 7.88 (1H, s), 8.25 (1H, d, J=3), 9.11 (1H, s), 11.18 (1H, s).

Found: M^+ 266

$C_{15}H_{14}N_4O$ requires 266.

Example 12

N-(1,4-Dimethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E12)

The title compound was prepared from 5-amino-1,4-dimethylindole (D17) and 3-pyridyl isocyanate (D4) following the procedure described in Example 2 Method B. This gave a yellow-green powder in 21% yield.

NMR (D_6-DMSO) δ:2.38 (3H, s), 3.76 (3H, s), 6.45 (1H, d, J=3), 7.24 (2H, s), 7.30 (1H, d, J=3), 7.89 (1H, dd, J=8,5), 8.33 (1H, d, J=8), 8.44 (1H, d, J=5), 8.67 (1H, s), 9.11 (1H, fine d), 10.3 (1H, b s).

Found: M^+ 280

$C_{16}H_{16}N_4O$ requires 280

Found: C, 57.8; H, 5.5; N, 16.9%. $C_{16}H_{16}N_4O$ .HCl.H_2O requires C, 54.4, H, 5.7; N, 16.7%

Example 13

N-(1-Methyl-1H-indol-5-yl)-N'-(2-chloropyrid-3-yl)urea hydrochloride (E13)

A stirred suspension of carbonyl diimidazole (0.34g, 2.1 mM) in dry dichloromethane (5 ml) was treated with a solution of 5-amino-1-methyl-1H-indole (D3) (0.29g, 2 mM) in dry dichloromethane (5 ml). After 0.25h the reaction mixture was evaporated to dryness, and the residue dissolved in dimethylformamide (10 ml). 3-Amino-2-chloro-pyridine (0.23g, 22 mM) was added to the reaction mixture which was heated to 90°C for 1h, then cooled and added to water (200 ml) with vigorous stirring. The precipitate was filtered, dried and recrystallised from ethanol affording the title compound as an off white solid (0.25g; 42%) which was converted to the hydrochloride salt using hydrogen chloride in ether, m.p. 155°C.

NMR (D_6-DMSO) δ:3.78 (3H, s), 6.37 (1H, d, J=5), 7.15 (1H, dd, J=12, 3), 7.30 (1H, d, J=5), 7.40 (2H, m), 7.72 (1H, d, J=3), 8.02 (1H, d, J=5), 8.49 (1H, d, J=3), 8.6 (1H, d, J=12), 9.34 (1H, s).

Found: M^+ 299, 301

$C_{15}H_{13}N_4O$ Cl requires 299, 301

Example 14

N-(1-Methyl-1H-indol-5-yl)-N'-(2-chloropyrid-5-yl)urea hydrochloride (E14)

The title compound was prepared in 60% yield from 5-amino-1-methyl-1H-indole (D3), carbonyl diimidazole and 5-amino-2-chloropyridine, using a procedure similar to that described in Example 13. m.p. 212°C.

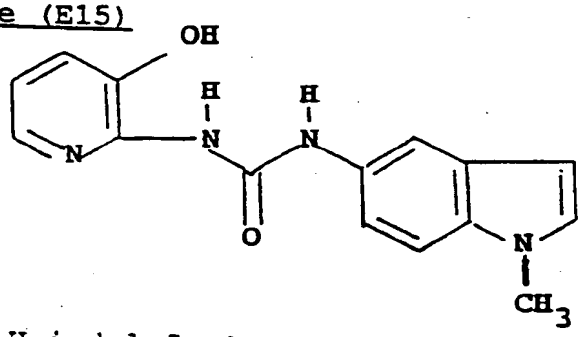
NMR (D_6-DMSO) δ:3.78 (3H, s), 6.32 (1H, d, J=5), 7.15 (1H, dd, J=12,3), 7.28 (1H, d, J=5), 7.40 (2H, m), 7.70 (1H, d, J=3), 8.00 (1H, dd, J=12,5), 8.50 (1H, d, J=5).

Found: M^+ 299, 301

$C_{15}H_{13}N_4OCl$ requires 299, 301.

Example 15

N-(1-Methyl-1H-indol-5-yl)-N'-(3-hydroxypyrid-2-yl)urea hydrochloride (E15)



E15

.HCl

N-(1-Methyl-1H-indol-5-yl)-N'-(3-benzyloxypyrid-2-yl)urea (D18) (0.37g, 1 mM) was hydrogenated for 2h in ethanol (40 ml) at atmospheric pressure and room temperature. The reaction mixture was filtered through kieselguhr, washed with ethanol. The filtrate was evaporated in vacuo to afford the title compound (0.21g, 74%) which was converted to the hydrochloride salt using hydrogen chloride in ether. m.p. 223°C.

NMR (D_6-DMSO) δ:3.78 (3H, s), 6.39 (1H, d, J=5), 6.95 (1H, m), 7.23 (2H, m), 7.3 (1H, d, J=5), 7.39 (1H, d, J=12), 7.83 (2H, m), 7.95 (1H, s).

Found: M^+ 282

$C_{15}H_{14}N_4O_2$ requires 282

Example 16

N-(1,3-Diethyl-2-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E16)

The title compound was prepared from the aminoindole (D21) and 3-pyridyl isocyanate (D4) using a procedure similar to that described for Example 2 Method B. The crude product was obtained in 79% yield. Recrystallisation from ethanol afforded the title compound, m.p. 192-193°C.

NMR (D_6 DMSO) δ:1.12 (3H, t, J=8), 1.20 (3H, t, J=8), 2.31 (3H, s), 2.65 (2H, q, J=8), 4.09 (2H, q, J=8), 7.02 (1H, dd, J=9,3), 7.26 (1H, d, J=9), 7.29 (1H, m), 7.63 (1H, d, J=3), 7.98 (1H, m), 8.17 (1H, m), 8.55 (1H, s), 8.60 (1H, d, J=3), 8.74 (1H, s).

Example 17

N-(1,2-Dimethyl-3-propyl-1H-indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E17)

The title compound was prepared from the aminoindole (D24) and 3-pyridyl isocyanate (D4) using a procedure similar to that described for Example 2 Method B, m.p. 132-134°C.

NMR (D_6-DMSO) δ:0.88 (3H, t, J=8), 1.54 (2H, m), 2.28 (3H, s), 2.58 (2H, m), 3.62 (3H, s), 7.04 (1H, d, J=4), 7.28 (1H,

d, J=6), 7.60 (1H, s), 7.90 (1H, m), 8.32 (1H, d, J=4), 8.45 (1H, d, J=6), 9.12 (1H, s), 9.25 (1H, s), 10.22 (1H, s).

Found: M^+ 322

$C_{19}H_{22}N_4O$ requires 322

Example 18

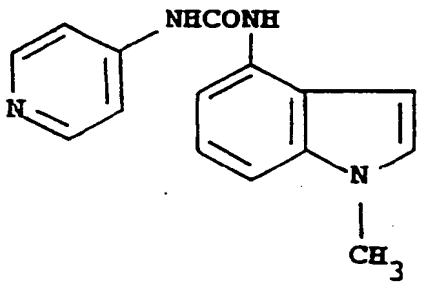
N-(1,2-Dimethyl-3-n-hexyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E18)

The title compound was prepared from the aminoindole (D27) and 3-pyridyl isocyanate (D4) using a procedure similar to that described for Example 2 Method B, the product being isolated as the free base.

NMR (D_6 DMSO) δ:0.84 (3H, m), 1.25 (6H, m), 1.52 (2H, m), 2.30 (3H, s), 2.62 (2H, m), 3.58 (3H, s), 7.05 (1H, dd, J=8, 2), 7.28 (1H, d, J=6), 7.60 (1H, s), 7.90 (1H, m), 8.32 (1H, m), 8.45 (1H, d, J=6), 9.15 (1H, m), 9.25 (1H, s), 10.15 (1H, s).

Example 19

N-(1-Methyl-1H-indol-4-yl)-N'-(4-pyridyl)urea hydrochloride (E19)



E19

.HCl

4-Amino-1-methyl-1H-indole (D10) (0.44g) was treated successively with phosgene (solution in toluene) and 4-aminopyridine as described in Example 1. The reaction

mixture was partitioned between dichloromethane and water, and filtered. The solid, the crude free base of the title compound, was filtered off and dried in vacuo. The filtrate was separated, and the organic portion was washed with brine, dried and evaporated to give an oil. The oil was chromatographed on silica using methanol/chloroform (0-10% methanol, gradient) as eluant, giving further crude free base.

The two portions of free base were combined, and this material (0.49g) was suspended in ethanol (50 ml) at reflux. Briefly after removing from the steam bath, HCl in ether (1.1 M, 3 ml) was added. The suspension was brought back to reflux, and then cooled. Filtration and drying gave the title compound (0.30g) as a grey-brown solid.

NMR (D_6-DMSO) δ:3.80 (3H, s), 6.87 (1H, d, J=3), 7.15 (2H, m), 7.32 (1H, d, J=3), 7.73 (1H, d, J=7), 7.95 (2H, d, J=6), 8.60 (2H, d, J=6), 9.76 (1H, s), 11.84 (1H, s), 14.5 (v broad).

Found: M^+ 266, $C_{15}H_{14}N_4O$ requires 266

Found: C, 55.89; H, 5.15; N, 17.20%
$C_{15}H_{14}N_4O.HCl.H_2O$ requires C, 56,16; H, 5.34; N, 17.47%

Example 20

N-(3-Ethyl-1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E20)

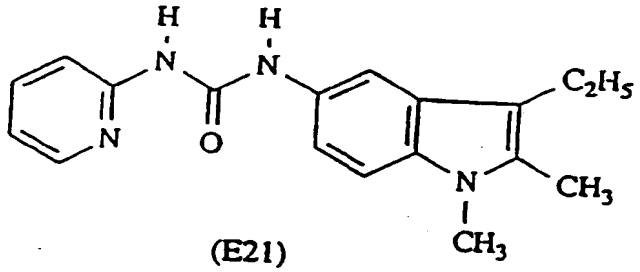
The title compound was prepared in 82% yield from the aminoindole (D32) and 3-pyridyl isocyanate (D4) using a procedure similar to that described for Example 2, Method B, the product being isolated as the free base.

NMR ($CDCl_3$) δ:1.26 (3H, t, J=7), 2.68 (2H, q, J=7), 3.69 (3H, s), 6.85 (1H, s), 7.04 (1H, m), 7.30 (2H, m), 7.56 (1H, s), 7.95 (1H, m), 8.15 (1H, m), 8.65 (2H, m), 8.80 (1H, s).

Found: M^+ 294, $C_{17}H_{18}N_4O$ requires 294

Example 21

N-(1,2-Dimethyl-3-ethyl-1H-indol-5-yl)-N'-(2-pyridyl)urea (E21)



(E21)

The title compound was prepared from the aminoindole (D1), phosgene and 2-aminopyridine using a procedure similar to that described for Example 1, the product being isolated as the free base, m.p. 120-123°C.

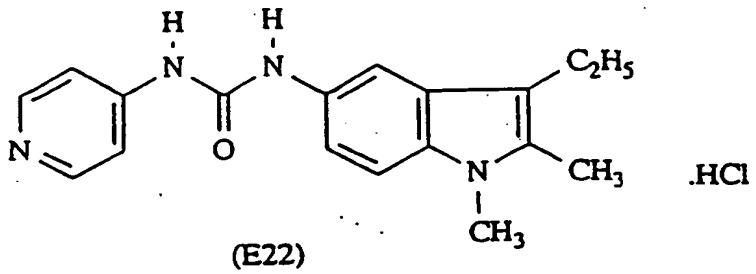
NMR ($CDCl_3$) δ: 1.22 (3H, t, J=8), 2.35 (3H, s), 2.73 (2H, q, J=8), 3.64 (3H, s), 6.91 (2H, m), 7.19 (1H, d, J=9), 7.28 (1H, m), 7.60 (1H, m), 7.77 (1H, m), 8.27 (2H, m), 11.5 (1H, broad s).

Found: C, 70.03; H, 6.36; N, 17.97%

$C_{18}H_{20}N_4O$ requires C, 70.11; H, 6.54; N, 18.17%

Example 22

N-(1,2-Dimethyl-3-ethyl-1H-indol-5-yl)-N'-(4-pyridyl)urea hydrochloride (E22)



(E22)

The title compound was prepared in 47% yield from the aminoindole (D1), phosgene and 4-aminopyridine using a procedure similar to that described for Example 1, the product being isolated as the hydrochloride salt, m.p. 237-243°C.

NMR (D_6 DMSO) δ: 1.12 (3H, t, J=8), 2.30 (3H, s), 2.62 (2H, q, J=8), 3.61 (3H, s), 7.05 (1H, dd, J=9,2), 7.29 (1H, d, J=9), 7.64 (1H, d, J=2), 7.90 (2H, d, J=6), 8.57 (2H, d, J=6), 9.67 (1H, broad s), 11.28 (1H, broad s).

Found: M^+ 308

$C_{18}H_{20}N_4O$ requires 308

Example 23

N-(1-Methyl-1H-indol-5-yl)-N'-(2-dimethylamino-5-pyridyl)urea (E23)

5-Amino-2-dimethylaminopyridine (D35) (0.137g; 1 mM) was stirred with 80% sodium hydride (66 mg; 2.2 mM) in dry dimethylformamide (5 ml) for 15 min at room temperature under nitrogen. The phenyl carbamate (D33) was then added and the mixture was stirred overnight at room temperature.

Solvent was then removed in vacuo and the residue was dissolved in dichloromethane/methanol, washed with water and brine, dried and evaporated. The residue was triturated with dichloromethane/petrol, and the solid material was chromatographed on silica gel and eluted with 2% methanol/dichloromethane. This gave the title compound (60 mg; 19%), m.p. 220-226°C.

NMR (D_6 DMSO) δ:2.98 (6H, s), 3.75 (3H, s), 6.32 (1H, d, J=3), 6.62 (1H, d, J=9), 7.11 (1H, d, J=8), 7.26 (1H, d, J=3), 7.31 (1H, d, J=8), 7.66 (2H, m), 8.10 (1H, d, J=3), 8.20 (1H, s), 8.38 (1H, s).

Found: M^+ 309

$C_{17}H_{19}N_5O$ requires 309

Example 24

N-(1,2-Dimethyl-3-isopropyl-1H-indol-5-yl)-N'-(3-pyridyl)urea hydrochloride (E24)

The title compound was prepared from the aminoindole (D38) and 3-pyridyl isocyanate (D4) using a procedure similar to that described for Example 2, Method B.

NMR (D_6 DMSO) δ: 1.42 (6H, d, J=7), 2.42 (3H, s), 3.22 (1H, m), 3.68 (3H, s), 7.12 (1H, m), 7.36 (1H, m), 7.90 (1H, s), 7.98 (1H, m), 8.38 (1H, m), 8.55 (1H, m), 9.20 (1H, s), 9.30 (1H, s), 10.22 (1H, s).

Found M^+ 322

$C_{19}H_{22}N_4O$ requires 322.

Example 25

N-(1,3-Diethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E25)

The title compound was prepared from ethyl 1,3-diethyl-5-nitro-1H-indole-2-carboxylate by hydrolysis and decarboxylation, then using a procedure similar to that in Description 3 and Example 2, Method B, the product being isolated as the free base.

m.p. 164-165°C

NMR ($CDCl_3$) δ:1.28 (3H, t, J=7), 1.45 (3H, t, J=7), 2.74 (2H, q, J=7), 4.12 (2H, q, J=7), 6.82 (1H, bs), 6.95 (1H, s), 7.10 (2H, m), 7.25 (2H, m), 7.58 (1H, s), 8.07 (1H, m), 8.24 (1H, m), 8.32 (1H, m).

Found: M^+ 308

$C_{18}H_{20}N_4O$ requires 308

Found: C, 69.93; H, 6.38; N, 17.98%

$C_{18}H_{20}N_4O$ requires C, 70.11; H, 6.54; N, 18.17%

Example 26

N-(3-Isopropyl-1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E26)

The title compound was prepared from ethyl 3-isopropyl-1-methyl-5-nitro-1H-indole-2-carboxylate by hydrolysis and decarboxylation, then using a procedure similar to that in Description 3 and Example 2, Method B, the product being isolated as the free base.

NMR ($CDCl_3$) δ:1.32 (6H, d, J=6), 3.15 (1H, m), 3.76 (3H, s), 6.76 (1H, bs), 6.88 (1H, s), 7.02 (1H, m), 7.13 (1H, m),

7.25 (2H, m), 7.60 (1H, m), 8.08 (1H, d, J=8), 8.22 (1H, m), 8.30 (1H, m).

Found: M^+ 308

$C_{18}H_{20}N_4O$ requires 308

Example 27

N-(1,3-Dimethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (E27)

The title compound was prepared from ethyl 1,3-dimethyl-5-nitro-1H-indole-2-carboxylate by hydrolysis and decarboxylation, then using a procedure similar to that in Description 3 and Example 2, Method B, the product being isolated as the free base.

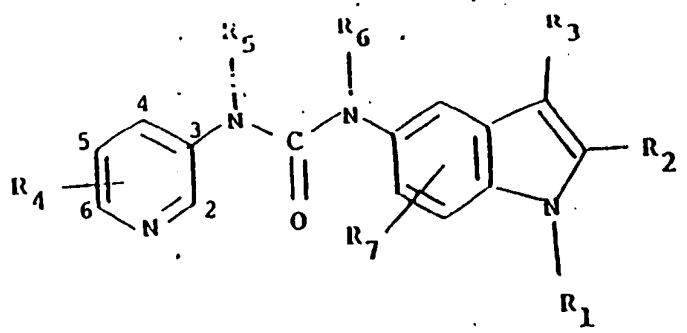
m.p. 210°C

NMR (D_6 - DMSO) δ: 2.25 (3H, s), 3.72 (3H, s), 6.88 (1H, s), 7.10 (1H, dd, J=9, 1), 7.22 (2H, m), 7.69 (1H, d, J=1), 8.04 (1H, m), 8.16 (1H, m), 8.31 (1H, s), 8.68 (1H, m).

Found: M^+ 280

$C_{16}H_{16}N_4O$ requires 280

TABLE 1



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Salt
E1	CH_3	CH_3	C_2H_5	H	H	H	H	HCl
E2	CH_3	H	H	H	H	H	H	HCl
E3	CH_3	CH_3	CH_3	H	H	H	H	HCl
E4	$(CH_2)_2CH_3$	H	H	H	H	H	H	$(COOH)_2$
E7	H	H	H	H	H	H	H	HCl
E8	CH_3	H	H	H	CH_3	H	H	-
E9	CH_3	H	H	H	H	CH_3	H	-
E10	CH_3	H	H	H	CH_3	CH_3	H	-
E12	CH_3	H	H	2-Cl	H	H	4-CH_3	HCl
E13	CH_3	H	H	6-Cl	H	H	H	HCl
E14	CH_3	H	H	H	H	H	H	HCl
E16	C_2H_5	CH_3	C_2H_5	H	H	H	H	-
E17	CH_3	CH_3	nC_3H_7	H	H	H	H	HCl
E18	CH_3	CH_3	nC_6H_{13}	H	H	H	H	-

TABLE 1 (CONTINUED)

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Salt
E20	CH_3	H	C_2H_5	H	H	H	H	-
E23	CH_3	H	H	6-$N(CH_3)_2$	H	H	H	-
E24	CH_3	CH_3	iC_3H_7	H	H	H	H	HCl
E25	C_2H_5	H	C_2H_5	H	H	H	H	-
E26	CH_3	H	iC_3H_7	H	H	H	H	-
E27	CH_3	H	CH_3	H	H	H	H	-

Pharmacological data

[^{3}H]-mesulergine binding to pig choroid plexus membranes in vitro

Evidence from the literature suggests that 5-HT_{1C} antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT_{1C} binding site can be determined by assessing their ability to displace [^{3}H]-mesulergine from 5-HT_{1C} binding sites in pig choroid plexus membranes. The method employed was similar to that of Pazos et al, 1984.

Pooled pig choroid plexi were homogenised in 20 vols of Tris HCl buffer (pH7.4) (containing 4mM $CaCl_2$ and 0.01% ascorbic acid) and centrifuged at 50,000g for 15 min at 4°C. The supernatant was removed and re-centrifuged. This was repeated a further two times with the incubation of the homogenate (37°C for 15 min) before the final centrifugation. The final pellet was resuspended in 20vols of buffer and stored at -70°C until use.

The tissue suspension (50µl) was incubated with [^{3}H]-mesulergine (2nM) in Tris HCl buffer (pH7.4) at 37°C (containing 0.01% ascorbic acid, 4mM $CaCl_2$) and 3 x 10^{-8}M spiperone for 30 minutes. Non-specific binding was measured in the presence of mianserin (10^{-6}M). Six concentrations of test drug (10^{-9} to 10^{-4}M final concentration) were added in a volume of 50µl. The total assay volume was 500µl. Incubation was stopped by rapid filtration using a Skatron

cell harvester and radioactivity measured by liquid scintillation spectrometry. The IC_{50} values were determined and the pK_i (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where

$$K_i = \frac{IC_{50}}{1 + \frac{C}{Kd}}$$

K_i = inhibition constant.

C = concentration of [^{3}H]-mesulergine

Kd = Affinity of mesulergine for 5-HT_{1C} binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.

Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.

Pazos, A. et al. (1984). Eur. J. Pharmacol., 106, 531-538.

Results are shown in Table 2.

Table 2

Compound	[^{3}H]-Mesulergine pK_i
E1	7.6
E2	6.8
E3	6.7
E4	6.7
E5	6.7
E6	6.5

Compounds of the remaining examples have a pK_i >5.

Rat stomach fundus

5-Hydroxytryptamine (5-HT) induces contractions of the rat stomach fundus through a 5-HT receptor that has the characteristics of a 5-HT_{1C} receptor (Blackburn et al, 1990). Hence, this tissue can be used to assess the 5-HT_{1C} antagonist actions of test drugs.

Rat stomach strips (6 x 4mm) were suspended under a 4g tension in 5ml baths containing Tyrode solution, gassed with a mixture of 95% O_2/5% CO_2. After a 1 hour equilibration period, two dose response curves were constructed to 5-HT (final concentrations, 10^{-9} to 3×10^{-6}M). Test drugs were then incubated at a final concentration of 10^{-6}M for 30 mins and another dose-response curve constructed to 5-HT. The apparent dissociation constant of a test drug, K_B, can be calculated from the equation where $K_B = \frac{[B]}{DR-1}$

where B = concentration of the test drug and DR = the dose ratio (the factor by which the concentration of the agonist has to be increased in the presence of the test drug to obtain an identical effect observed in the absence of the test drug).

The results are shown in Table 3

Blackburn et al. (1990). Eur. J. Pharmacol., 180, 229-237.

Table 3

Compound	K_B
E1	3.2×10^{-8}M
E2	1×10^{-7}M
E3	2.5×10^{-8}M
E4	4.0×10^{-7}M
E5	2.5×10^{-7}M
E6	1.7×10^{-7}M

Social Interaction Test

Potential anxiolytic properties have been evaluated using the social interaction test based on that described by File (1980 J.Neurosci.Meth., 2, 219). Active social interaction between male rats is usually quantitated by counting interactive behaviours such as following, grooming, sniffing, climbing over or under, biting, mounting and boxing. This behaviour is supressed when the rats encounter each other in an environment which is novel and brightly lit. Under these circumstances anxiolytic drugs will enhance the level of social interaction.

Rats were housed in groups of 8 in a holding room adjacent to the experimental chamber for 8 days. They were then housed singly in the same room for 3 days prior to the experimental day. On the experimental day rats were injected p.o. 1h pretest with vehicle or drug in pairs at 15 min intervals beginning at 10.00 am. 60 Mins later they were placed with a weight matched pair mate (encountered for the first time) in the social interaction box in a separate room. The box was made of white perspex 54 x 37 x 26 cm

with no lid. The floor was divided into 24 equal squares and the cage was brightly lit. Active social interaction was scored blind over the next 15 min by remote video monitoring to give total interaction scores. The number of squares crossed by each rat was also scored and summed. At the end of each test the box was carefully wiped with a damp cloth. Unlike anxiolytic drugs, treatments that enhance social interaction by stimulant action will also increase locomotion. Treatments that are sedative reduce locomotion.

Test Results

The compound of Example 2 showed a significant increase in social interaction at doses of 2-40 mg/kg.

Geller-Seifter Procedure

Potential anxiolytic properties are evaluated using the Geller-Seifter procedure based on that originally described by Geller and Seifter, (1960) Psychopharmacologia, 1, 482-492. This procedure has been shown to be selective for drugs with anxiolytic properties (Cook and Sepinwall, (1975) ''Mechanism of Action of Benzodiazepines'' ed. Costa, E. and Greengard, P., Raven Press, New York, pp. 1-28).

Rats are trained on a variable interval 30 sec schedule (VI30) to press a lever in order to obtain food reward. The 5 min sessions of the VI30 schedule alternate with 2-5 min of a schedule (FR5) in which every 5th lever press is followed by presentation of a food pellet paired with a 0.5 sec mild footshock. The total study lasts approximately 30 mins. Rats typically respond with high rates of lever pressing under the VI30 schedule and low response rates under the FR5 'conflict' session. Anxiolytic drugs increase

the suppressed response rates of rats in a 'conflict' session.

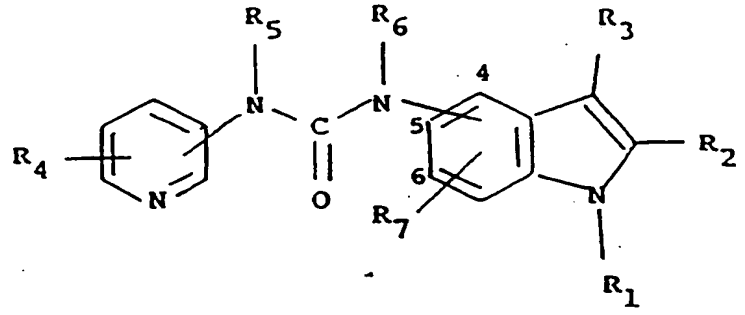
Drugs are administered intraperitoneally or orally to groups of 3-8 rats 30 min before testing.

The results are expressed as the percentage increase in the square root of the total number of lever presses in the FR5 'conflict' session. Square root transformation is necessary to normalise the data for statistical analysis using parametric methods.

The compound of Example 2 showed a significant increase in responding in the 'conflict' session at dose levels in the range 5-40 mg/kg p.o.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1, R_2 and R_3 are independently hydrogen or C_{1-6} alkyl;
R_4 is hydrogen, C_{1-6} alkyl, halogen, hydroxy or NR_8R_9 where R_8 and R_9 are independently hydrogen or C_{1-6} alkyl;
R_5 and R_6 are independently hydrogen or C_{1-6} alkyl; and
R_7 is hydrogen, C_{1-6} alkyl or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole ring.

2. A compound according to claim 1 wherein the urea moiety is attached at the 3-, 4- or 5-position of the pyridine ring.

3. A compound according to claim 1 or 2 wherein the urea moiety is attached at the 4- or 5-position of the indole ring.

4. A compound according to any preceding claim wherein any alkyl moiety within variables R_1 to R_9 is C_{1-3} alkyl.

5. A compound according to claim 4 wherein R_1 is methyl, R_2 is methyl or hydrogen, R_3 is hydrogen, methyl, ethyl, n-propyl or iso-propyl, R_4 is hydrogen and R_5, R_6 and R_7 are independently hydrogen or methyl.

6. N-(1,2-Dimethyl-3-ethyl-1H-indol-5-yl)-N'-(3-pyridyl)-urea.

7. N-(1-Methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

8. N-(1,2,3-Trimethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

9. N-(1-Propyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

10. N-(1-Methyl-1H-indol-4-yl)-N'-(3-pyridyl)urea.

11. N-(1-Methyl-1H-indol-6-yl)-N'-(3-pyridyl)urea.

12. N-(1H-Indol-5-yl)-N'-(3-pyridyl)urea.

13. N-(1-Methyl-1H-indol-5-yl)-N'-methyl-N'-(3-pyridyl)urea.

14. N-Methyl-N-(1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

15. N-Methyl-N-(1-methyl-1H-indol-5-yl)-N'-methyl-N'-(3-pyridyl)urea.

16. N-(1-Methyl-1H-indol-5-yl)-N'-(2-pyridyl)urea.

17. N-(1,4-Dimethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

18. N-(1-Methyl-1H-indol-5-yl)-N'-(2-chloropyrid-3-yl)urea.

19. N-(1-Methyl-1H-indol-5-yl)-N'-(2-chloropyrid-5-yl)urea.

20. N-(1-Methyl-1H-indol-5-yl)-N'-(3-hydroxypyrid-2-yl)urea.

21. N-(1,3-Diethyl-2-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

22. N-(1,2-Dimethyl-3-propyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

23. N-(1,2-Dimethyl-3-n-hexyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

24. N-(1-Methyl-1H-indol-4-yl)-N'-(4-pyridyl)urea.

25. N-(3-Ethyl-1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

26. N-(1,2-Dimethyl-3-ethyl-1H-indol-5-yl)-N'-(2-pyridyl)urea.

27. N-(1,2-Dimethyl-3-ethyl-1H-indol-5-yl)-N'-(4-pyridyl)urea.

28. N-(1-Methyl-1H-indol-5-yl)-N'-(2-dimethylamino-5-pyridyl)urea.

29. N-(1,2-Dimethyl-3-isopropyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

30. N-(1,3-Diethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

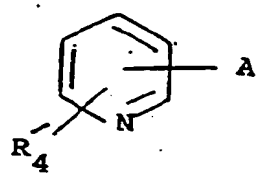
31. N-(3-Isopropyl-1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

32. N-(1,3-Dimethyl-1H-indol-5-yl)-N'-(3-pyridyl)urea.

33. A pharmaceutically acceptable salt of a compound according to any one of claims 6 to 32.

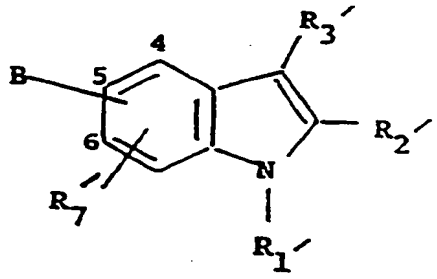
34. A process for the preparation of a compound according to claim 1, which process comprises:

(a) the coupling of a compound of formula (II);



(II)

with a compound of formula (III);

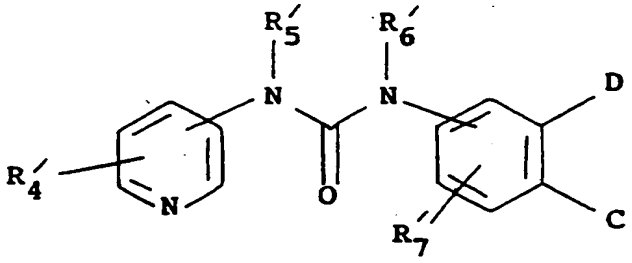


(III)

wherein B is attached at the 4-, 5- or 6-position of the indole ring and A and B contain the appropriate functional group(s) necessary to form the moiety $-NR_5'CONR_6'-$ when coupled, wherein R_5' and R_6' are R_5 and R_6 as defined in claim 1 or groups convertible thereto, and the variables R_1', R_2', R_3', R_4' and R_7' are R_1, R_2, R_3, R_4 and R_7 respectively, as defined in claim 1, or groups convertible thereto, and thereafter optionally and as necessary and in

any appropriate order, converting any R_1', R_2', R_3', R_4', R_5', R_6' and R_7' when other than R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively to R_1, R_2, R_3, R_4, R_5, R_6 and R_7, interconverting R_1, R_2, R_3, R_4, R_5, R_6 and R_7, and forming a pharmaceutically acceptable salt thereof, or

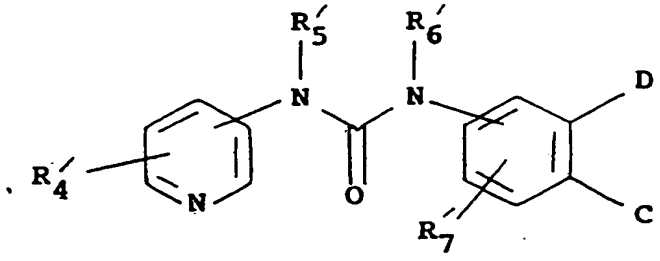
(b) cyclising a compound of formula (IV):



(IV)

wherein R_4', R_5', R_6' and R_7' are as defined in formulae (II) and (III) and C and D contain the appropriate functional group(s) necessary to form the indole ring substituted by R_1', R_2' and R_3' as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5', R_6' and R_7' when other than R_1, R_2, R_3, R_4, R_5, R_6 and R_7, to R_1, R_2, R_3, R_4, R_5, R_6 and R_7, interconverting R_1, R_2, R_3, R_4, R_5, R_6 and R_7 and forming a pharmaceutically acceptable salt.

35. A compound of formula (IV):



(IV)

wherein R_4', R_5', R_6' and R_7' are R_4, R_5, R_6 and R_7 as defined in claim 1 or groups convertible thereto and C and D contain the appropriate functional group(s) necessary to form an indole ring substituted by R_1, R_2 and R_3 as defined in claim 1 or groups convertible thereto.

36. A pharmaceutical composition which comprises a compound according to claim 1 and a pharmaceutically acceptable carrier.

37. A compound according to claim 1 for use as a therapeutic substance.

38. A compound according to claim 1 for use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia.

39. A method of treatment or prophylaxis of anxiety, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound according to claim 1.

40. The use of a compound according to claim 1 in the manufacture of a medicament for the treatment or prophylaxis of anxiety, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00381

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D401/12; A61K31/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 29, no. 11, 1986, WASHINGTON US pages 2415 - 2418 P. FLUDZINSKI '2,3-Dialkyl(dimethylamino)indoles: interaction with 5HT1, 5HT2, and rat stomach fundal serotonin receptors.' cited in the application * page 2415 * ---	1,38
E	WO,A,9 205 170 (BEECHAM GROUP PLC) 2 April 1992 * complete document * -----	1-40

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23 SEPTEMBER 1992	11. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200381 SA 57177

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 23/09/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9205170	02-04-92	None	